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| **Liver and its Diseases** | | | | ©2013 Doris Kim | | |
| **Type** | **Pathogenesis** | | **Clinical** | | | **Labs/Histology** |
| ***Liver Histology*** | - Cords of hepatocytes  - Blood flows through sinusoids lined by discontinuous endothelium  - Space of Disse: where microvilli from hepatocytes extend  - Kupffer cells: attached to blood flow surface of endothelium; mo of liver  - Ito cells: contain fat and in Space of Disse  - Canaliuli: between hepatocytes; part of biliary tree | | Blood supply:  70% from portal vein  30% from hepatic artery | | |  |
| ***Hepatic Failure***  ***Acute hepatic failure***  ***Chronic hepatic failure*** | Causes massive necrosis  Drugs: acetaminophen, halothane, rifampin  Toxins: carbon tetrachloride, mushrooms  Infections: viral hepatitis (A and B)  Cirrhosis | | Clinical features:  1. Jaundice  2. Hypoalbuminemia  3. Hyperammonemia  4. Hyperestrogenemia  - Palmar erythema (local vasodilation)  - Spider angiomas  - Hypogonadism, gynecomastia in males | | | 5. Coagulopathies  6. Hepatic encephalopathy (elevated blood ammonia), impairement of neuronal functions  7. Hepatorenal syndrome: renal failure due to bilirubin damaging tubules  8. Portal HTN -> esophageal varices |
| **Hepatitis** | | | |  | | |
| **Type** | **Pathogenesis** | **Outcomes** | | | **Diagnosis/Histology** | |
| ***Hepatitis A*** | * ssRNA virus (icosahedral capsid) (picorna) * Mild, self-limiting * Incubation: 2-6 weeks * Fecal-oral transmission (contaminated food or water)   *Carrier status:* no clinical symptoms, but can transmit organisms; diagnosed by elevated serum enzymes and serology | * No chronic disease * Can be fulminant | | | IgM antibody acute phase  IgG antibody indicates immunity | |
| ***Hepatitis B*** | * dsRNA (enveloped) (hepadna) * Incubation: 4-26 weeks * Parenteral transmission; sexual | * Subclinical disease w. recovery (maj.) * Acute hepatitis with resolution * Chronic hepatitis: cirrhosis or carrier status * Fulminant hepatitis * Hepatocellular carcinoma | | |  | |
| ***Hepatitis C*** | * ssRNA (enveloped) (Flavi) * Incubation: 2-26 weeks * Parenteral transmission; intranasal | * Acute hepatitis with resolution * Chronic hepatitis (majority) * Fulminant very rare * Cirrhosis * Hepatocellular carcinoma | | | HCV RNA in acute phase for 1-3 weeks  HCV antibodies after 3-6 weeks  Fatty accumulation in hepatocytes | |
| ***Hepatitis D*** | * Circular defective ssRNA * Pareneteral transmission | Coinfection: Pre-existing Hep B + Hep D   * 5% chronic liver disease   Superinfection: Hep B + Hep B infection  70% chronic liver disease | | | Detect IgM and IgG antibodies  HDV RNA serum  HDAg in liver | |
| ***Hepatitis E*** | * ssRNA (Calicivirus) (enveloped) * Fecal-oral transmission * Incubation: 4-5 weeks | * Acute hepatitis * Never chronic disease * High mortality among pregnant women | | | PCR HEV RNA  Detection of serum IgM and IgG antibodies | |
| ***Acute Viral Hepatitis*** | HBV: ground glass appearance due to spheres and tubules of HBsAg  HBV hepatocytes sometimes has “sanded” appearance due to HBcAg; indicating active viral replication  Cholestasis: inconsistent finding  Dropout necrosis: due to cell rupture with macrophages  Apoptotic bodies = hepatitis  Inflammation: kupffer cells hypertrophy and hyperplasia  Bile duct proliferation  Ballooning degeneration = active hepatitis | groundglass  HepatitisM | | | robbins | |
| ***Chronic Viral Hepatitis*** | * Symptomatic, biochemical or serologic evidence of ongoing or relapsing disease > 6 months with histologic documentation   Clinical course: unpredictable   * Spontaneous recovery -> rapid progression to cirrhosis   Major causes of death:   * Cirrhosis * Liver failure * Massive hematemesis (portal HTN) * Hepatocellular carcinoma   *Chronic persistent hepatitis*   * Periportal fibrosis * Can remain dormant for years   *Chronic active hepatitis*   * Bridging fibrosis between lobules * Cirrhosis and carcinoma   *More advanced cirrhosis*  1. **Bridging** - delicate bands of fibrous CT replace adjacent lobules  2. **Parenchymal nodules** - due to regeneration of encircling hepatocytes; small (micronod.)< 3cm - large (macronod.) several cm.  3. **Disruption of architecture**  4. **Diffuse injury** - has to be throughout liver  5. **Nodularity** - balance between regeneration and scarring  6. **Fibrosis** - irreversible  7. **Vascular architecture reorganized** - due to parenchymal injury and scarring, abnormal interconnections between vascular inflow and hepatic vein outflow channels | Mildest forms significant inflammation limited to portal tracts e.g. lymphs, plasma cells, mo  Lymphoidaggregateviral hep When progressive get bridging necrosis and fibrosis that extends beyond limiting plate and links portal to portal or portal to terminal hepatic venule leading to cirrhosis  piecemealnecrosis | | | robbinspostnecroticcirrM | |
| ***Fulminant Hepatitis*** | * When hepatic insufficiency progresses from onset of symptoms to hepatic encephalopathy within 2-3 weeks | 50% due to viral hepatitis  50% due to chemical toxicity  Acetaminophen, isoniazide, MOIs, halothane, methyldopa mycotoxins | | | **Morphology**  1. Massive to submassive necrosis (diffuse to patchy necrosis)  2. Shrunken liver with collapse of architecture with little to no inflammation.  2. Some regeneration if patient survives for a while. | |
| ***Autoimmune Hepatitis*** | * Indistinguishable form viral hepatitis clinically * Responds well to anti-inflammatory drugs * 60% have other autoimmune diseases (RA, thyroiditis, Sjogren syndrome, UC) * Women (70%) * Elevated IgG * HLA-B8 or HLA-Drw3 | **Type 1:**  + ANA  + SMA (smooth muscle antibody)  + AAA (anti actin antibody)  Soluble anti liver  Anti pancreas antigen  Antibodies  SLA/LP | | | **Type 2:**  Anti-KLM-1 (kidney-liver-microsome)  Anti-CYP2D6  ACL-1 (anti-liver cytosol) \*most common epitope | |
| **Metabolic Liver Diseases** | **Pathogenesis** | **Pathogenesis/Clinical Features** | | | **Labs/Histology** | |
| ***Non Alcoholic Fatty Liver Disease***  ***(NAFLD)***  *Most common cause of chronic liver disease* | Classification   * Simple hepatic steatosis * Steatosis with minimal inflammation * Non alcoholic steatohepatitis (NASH)   NAFL and NASH:   * Obesity, insulin resistance/hyperinsulinemia * Dyslipidemia, Type 2 diabetes * Principal cause of cryptogenic cirrhosis | Two Hit Hypothesis  Hepatic fat accum. + hepatic oxidative stress  Oxidative stress acts on accumulated lipids 🡪 lipid peroxidation, reactive oxygen 🡪 cell damage | | |  | |
| ***Hemochromatosis***  *Hepcidin deficiency*  *Mutation of HFE gene (chromosome 6)*  *(C282Y most common)* | * Accumulation of iron in parenchymal cells in multiple organs * Iron overloaded state   🡪 Release of iron from enterocytes and macrophages   * Excess iron 🡪 toxicity to host tissues   Lipid peroxidation, iron catalyzed  Free radicals Stimulation of collagen formation | * Arthralgia * Erectile dysfunction * Diabetes * Arrhythmias * Skin pigmentation (bronze skin) (increased pituitary hormones)   “bronze diabetes”  Complications: cirrhosis | | | Diagnosis:  Increased serum Fe, ferritin  Decreased hepcidin | |
| ***Hemosiderosis*** | * Iron accumulation in kupffer cells * Secondary to transfusions * No cirrhosis |  | | |  | |
| ***Wilson’s Disease***  *ATP7B mutation* | * Copper accumulation in brain, liver, eye * Copper circulates bound to ceruloplasmin   Adolescent with hepatic failure and neuro def. | * Parkinson like disease * Liver disease * Kayser-Fleischer rings (green/yellow ring around cornea) | | | Diagnosis:  Decreased ceruloplasmin  Excess copper in liver and urine | |
| ***Alpha-1-Antitrypsin Deficiency***  *🡪 emphysema*  *🡪 liver disease* | * Alpha-1-AT is a protease inhibitor | * Neonatal hepatitis * Cirrhosis * Late onset hepatitis * Emphysema | | | PAS + intrahepatic inclusions (cytoplasmic) | |

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| **Alcoholic Liver Disease** | **Pathogenesis** | **Pathogenesis/Clinical Features** | **Labs/Histology** |
| ***Alcoholic liver disease*** | Etiology:   * Daily intake of 80gm+ (8 beers) severe risk of hepatic injury * 10-15% of alcoholics develop cirrhosis | Hepatocellular injury:   * Induction of cytochrome p450 * Free radical formation * Alcohol toxic to microtubular and mt fxn * Acetaldehyde induces lipid peroxidation and acetaldehyde protein adduct formation * Alcohol induces immunologic attack on hepatic neonatigens * Collagen stimulated by inflammatory cytokines or those from kupffer cells |  |
| ***Hepatic steatosis*** | * Fatty change * Perivascular fibrosis   Shunting of normal substrates away from catabolism and to lipid biosynthesis due to:   * Increased NADH and acetaldehyde dehydrogenase * Impaired assembly and secretion of lipoproteins * Increased peripheral catabolism of fat | * No signs or symptoms * Mild swelling with elevation of bilirubin and alkaline phosphatase |  |
| ***Alcoholic Hepatitis*** | * Liver cell necrosis * Inflammation * Mallory bodies * Fatty change | * Variable with 10-20% of death * Cirrhosis with repeated bouts |  |
| ***Cirrhosis*** | * Irreversible fibrosis * Hyperplastic nodules * Bridging fibrous septa * Parenchymal nodules * Disruption of entire liver architecture * Diffuse parenchymal injury and ultimate fibrosis * Nodularity * Reorganization of vascular architecture   Pathogenesis: activation of perisnusoidal stellate cells 🡪 cytokines  *Progressive fibrosis and reorganization by:*   * Chronic inflammation producing cytokines * Cytokine production by activated Kupffer cells * Disruption of extracellular matrix * Direct stimulation by toxins (alcohol)   *This activation leads to:*   * Robust mitotic activity * Shifting from the resting state lipocyte phenotype to transitional myofibroblast phenotype * Increased capacity for synthesis and secretion of extracellularmatrix | Clinical Features:   * Portal hypertension -> esophageal varices, hypersplenism -> pancytopenia * Jaundice, ascites, abnormal labs * May be clinically silent   *Redistribution of vasculature within newly formed fibrous septa:*   * Loss of fenestration in sinusoidal endothliu * Blocks hepatocellular secretion of proteins and other solutes * Compress and strangulate hepatocytes * Less enzymes released, lose liver function * See fibrosis and collagen deposition (I, III, IV)   Complications:  *1. Portal HTN*   * Ascites, esophageal varices, GI bleeds, caput meduase, hepatic encephalopathy * Portosystemic shunt   *2. Hepatocellular carcinoma*  *3. Hypersplenism and pancytopenia* | Etiology:  Alcoholic liver disease - 60-70%  Viral hepatitis - 10%  Biliary diseases - 5-10%  Primary hemochromatosis - 5%  Wilson disease - rare  α1-Antitrypsin deficiency - rare  Cryptogenic (idiopathic) - 10-15%  Steatohepatitis (NAFL) |

**Hepatitis B**

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|  | **HbsAg** | **HbeAg** | **HbcAg** | **Hbs Antibody** |
| **Acute** | **+** first to rise | **+** indicates infectivity | IgM | -- |
| **Window** | **--** | -- | IgM | -- |
| **Resolved** | **--** | **--** | IgG | IgG |
| **Chronic** | **+** (after 6 mo) | +/-- | IgG | -- |
| **Immunization** | **--** | **--** | **--** | IgG |

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| **Patterns of Injury in Drug- and Toxin-Induced Hepatic Injury** | | |
| **Patterns of Injury** | **Morphologic Findings** | **Examples of Associated Agents** |
| **Cholestatic** | Bland hepatocellular cholestasis, without inflammation | Contraceptive and anabolic steroids  Estrogen replacement therapy |
| **Cholestatic hepatitis** | Cholestasis with lobular necroinflammatory activity; may show bile duct destruction | Numerous antibiotics  Phenothiazines |
| **Steatosis** | Macrovesicular | Ethanol, methotrexate, cortiocosteroids, total parenteral nutrition |
| **Steatohepatitis** | Microvesicular  Mallory bodies | Amiodarone  Ethanol |
| **Fibrosis and cirrhosis** | Periorbital and pericellular fibrosis | Methotrexate, Isoniazid, Enalapril |
| **Granulomas** | Noncaseating epithelioid granulomas | Sulfonamides |
| **Vascular lesions** | Sinusoidal obstruction syndrome (veno-occlusive disease)   * Obliteration of central vein   Budd Chiari syndrome (emergency)   * Hepatic vein thrombosis * Abdominal pain, ascites, hepatomegaly * Paroxysmal nocturnal hemoglobinuria * Passive congestion (cardiac sclerosis)   Peliosis hepatis:   * Primary dilation of sinusoids * Blood filled cavities not lined by endothelial cells * Usually asymptomatic * If severe, intraabdominal hemorrhage | High dose chemotherapy  Bush teas  Oral contraceptives  Anabolic steroids  Tamoxofin |
| **Neoplasms** | Hepatic adenoma  Hepatocellular carcinoma  Cholangiocarcinoma  Angiosarcoma | Oral contraceptives  Anabolic steroids  Thorotrast  Thorotrast  Thorotrast, vinyl chloride |

Microvesicular steatorrhea- tetracycline, Reyes syndrome, pregnancy, amiodorone

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| **Hepatic Disease in Pregnancy** | **Pathogenesis** |
| ***Preclampsia and Eclampsia***  *HELLP Syndrome* | * Hemolysis * Elevated liver enzymes * Low platelets * DIC |
| ***Acute fatty liver of pregnancy*** | * Microvesicular fat |
| ***Intrahepatic Cholestasis***  *Caused by hormonal changes during pregnancy* | * Pruritis in 3rd trimester * Jaundice * Dark urine * Light stools |